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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/112,041	07/08/98	GHETIE M	UTSD:521/WIM

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EXAMINER	
NICHOLS, J	

ART UNIT	PAPER NUMBER
1642	13

DATE MAILED: 02/14/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/112,041	Ghetie et al.
Examiner	**Group Art Unit**
Jennifer Nichols, Nee Hunt	1642

☒ Responsive to communication(s) filed on *Nov 15, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-52* is/are pending in the application.

Of the above, claim(s) *26-42* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-25 and 43-52* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3, 8, 9, 11*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Claims 26-42 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 13.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 3-7, 13-21, 45, and 48-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-6, 13-20, 45, and 48 are unclear in the recitation of an antibody which "asserts" ... anti-neoplastic activity. The metes and bounds of "asserts" cannot be determined from the claims or specification as recited. The qualities and activities encompassed by "asserts" cannot be determined.

Claim 6, 18-20, and 48 are unclear in the recitation of "substantially no" anti-neoplastic activity. The metes and bounds of "substantially no" cannot be determined. It is not possible to determine what parameters or quantities are encompassed by "substantially no".

Claims 7, 21, and 59 are unclear in the recitation of hypercrosslinking. The metes and bounds of hypercrosslinking cannot be determined. The methods and properties of hypercrosslinking cannot be determined from the claims or specification.

Claim 9 is improper because the recitation of "the IgG" lacks antecedent basis.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-6, 10-20, 24-25, 43-48, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by *Ahlem et al., US Patent 5,273,743, December 28, 1993.*

Ahlem et al. teaches a conjugate of two, three, or more monoclonal antibodies wherein none of the monoclonal antibodies comprise an Fc region. Ahlem et al. also teaches the said conjugate which comprises an antibody which asserts anti-neoplastic activity in conjugated form. Ahlem et al. teaches conjugates which comprise an anti-Her2, anti-breast tumor, anti-ovarian tumor, anti-prostate tumor, and/or anti-lung tumor antibody (the conjugates comprise antibodies which bind tumor markers EGFR, specific for breast, ovarian, and lung cancer, see *Cancer Biology, 1995, page 348, 3rd paragraph*, and PSA which bind prostate cancer cells). Ahlem et

al. also teaches the said conjugate which comprises an antibody which does not assert anti-neoplastic activity in unconjugated form. Ahlem et al. teaches homo and heteroconjugates. (see abstract and column 13, line 43-column 14, line 51)

Ahlem et al. also teaches a method of making any of the aforementioned conjugates, as well as conjugates in which the first and second antibodies assert anti-neoplastic activity in conjugated form.(column 6, line 7- column 9, line 55) Ahlem et al. also teaches method of making conjugates in which none of the antibodies assert anti-neoplastic activity in an unconjugated form.

Ahlem et al. also teaches a pharmaceutical composition comprising a conjugate comprising a monoclonal antibody and a pharmaceutically acceptable carrier, wherein no monoclonal antibody comprises an Fc region.(column 19, lines 36-59) The monoclonal antibody asserts anti-neoplastic activity in conjugated form. Ahlem et al. teaches conjugates which comprise an anti-Her2, anti-breast tumor, anti-ovarian tumor, anti-prostate tumor, and/or anti-lung tumor antibody. Ahlem et al. also teaches the said conjugate which comprises an antibody which does not assert anti-neoplastic activity in unconjugated form. Ahlem et al. teaches homo and heteroconjugates. (see abstract and column 13, line 43-column 14, line 51)

5. Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by *Hudson, Bio/technology, Vol 12, July 1994.*

Hudson teaches a conjugate of two, three, or more monoclonal antibodies wherein none of the monoclonal antibodies comprise an Fc region. Hudson also teaches the said conjugate which comprises an antibody which asserts anti-neoplastic activity in conjugated form. Hudson teaches conjugates which comprise an anti-CD-19, anti-breast tumor, anti-ovarian tumor, and anti-lung tumor antibody (the conjugates comprise antibodies which bind tumor markers specific for breast, ovarian, and lung cancer, see *Cancer Biology, 1995, page 348, 3rd paragraph*) Hudson also teaches the said conjugate which comprises an antibody which asserts no anti-neoplastic activity in unconjugated form.(page 550, first paragraph and page 551, second paragraph)

6. Claims 1-3, 6, 8-9, 11-15, 18-20 and 22-23, 25, 43-45, 48, and 50-51 are rejected under 35 U.S.C. 102(b) as being anticipated by *Glennie, WO 91/03493, March 21, 1991.*

Glennie teaches a conjugate of two, three, or more monoclonal antibodies wherein none of the monoclonal antibodies comprise an Fc region. Glennie also teaches the said conjugate which comprises an antibody which asserts anti-neoplastic activity in conjugated form. Glennie also teaches the said conjugate which comprises an antibody which does not assert anti-neoplastic activity in unconjugated form (abstract and page 1-page 3). The conjugate comprises a monoclonal antibody which is a mammalian IgG monomer (page 7, last paragraph).

Glennie also teaches a method of making any of the aforementioned conjugates, as well as conjugates in which the first and second antibodies assert anti-neoplastic activity in conjugated

form. Glennie also teaches method of making conjugates in which none of the antibodies assert anti-neoplastic activity in an unconjugated form.(page 3, line 28-page 5, and page 8-9)

Glennie also teaches a pharmaceutical composition comprising a conjugate comprising a monoclonal antibody and a pharmaceutically acceptable carrier, wherein no monoclonal antibody comprises an Fc region. The monoclonal antibody asserts anti-neoplastic activity in conjugated form. Glennie also teaches the said conjugate which comprises an antibody which does not assert anti-neoplastic activity in unconjugated form. The conjugate comprises a monoclonal antibody which is a mammalian IgG monomer (page 19-23)

7. Claims 1-3, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by *Ghetie et al., Exp. Opin. Invest. Drugs, Vol 5, No 3, pages 309-321.*

Ghetie et al. teaches a conjugate of two, three, or more monoclonal antibodies wherein none of the monoclonal antibodies comprise an Fc region. Ghetie et al. also teaches the said conjugate which comprises an antibody which asserts anti-neoplastic activity in conjugated form. Ghetie et al. also teaches the said conjugate which comprises an antibody which does not assert anti-neoplastic activity in unconjugated form (page 314, last paragraph- 315, 1st paragraph)

8. Claims 1-3 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by *Bosslet et al., US Patent 5,591,828, January 7, 1997.*

Bosslet et al. teaches a conjugate of two, three, or more monoclonal antibodies wherein none of the monoclonal antibodies comprise an Fc region. Bosslet et al. also teaches the said conjugate which comprises an antibody which asserts anti-neoplastic activity in conjugated form. Bosslet et al. also teaches the said conjugate which comprises an antibody which does not assert anti-neoplastic activity in unconjugated form. (Figure 1-4 and column 1, lines 12-16 and column 2, lines 7-32)

9. Claims 1-2, 6, 10-12, 18-20, and 23-24 are rejected under 35 U.S.C. 102(b) as being anticipated by *Cumber et al., The Journal of Immunology, Vol 149, pages 120-126, July 1, 1992.*

Cumber et al. teaches a conjugate of two, three, or more monoclonal antibodies wherein none of the monoclonal antibodies comprise an Fc region. Cumber et al. also teaches the said conjugate which comprises an antibody which does not assert anti-neoplastic activity in unconjugated form. Cumber et al. also teaches a method of making any of the aforementioned conjugates. Cumber et al. also teaches method of making conjugates in which none of the antibodies assert anti-neoplastic activity in an unconjugated form. (See abstract and materials and methods, page 120)

10. Claims 1, 3, 9, 11, 13, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by *Bagshawe et al., US Patent 5,683,694, November 4, 1997.*

Bagshawe et al. teaches a conjugate comprising a monoclonal antibody that does not comprise an Fc region. The conjugate exhibits antineoplastic activity. (Column 1, lines 14-20, and column 2, lines 24-40) Bagshawe also teaches how to make the aforementioned conjugate using a mammalian monoclonal antibody (column 7- 8).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-7, 10-21, 24-25, 43-49, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Ahlem et al., US Patent 5,273,743, December 28, 1993*, in view of *Marches et al., Therapeutic Immunology, Vol 2, pages 125-136, 1995, or Racila et al, Journal of Experimental Medicine, Vol 181, pages 1539-1550, 1995.*

Ahlem et al. teaches as applied to claims 1-6, 10-20, 24-25, 43-48, and 52 supra. Ahlem et al. fails to teach hypercrosslinking to make the antibody conjugates.

Marches et al. teaches that hypercrosslinking of antibody conjugates induces a significant increase in cell cycle arrest and apoptosis in virtually all antibodies.(see page 130, "Effect of Crosslinking IgM on lymphoma cells"). Racila et al. teaches that hypercrosslinking increases apoptosis. (See abstract)

Therefor it would have been prima facie obvious to one of ordinary skill in the art to combine the antibody conjugate of Ahlem et al. by hypercrosslinking, as taught by Marches et al. or Racila et al. and one would have been motivated to do so because hypercrosslinking increases cell cycle arrest and apoptosis, as taught by Marches et al. and Racila et al.

13. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Hudson, Bio/technology, Vol 12, July 1994.* in view of *Marches et al., Therapeutic Immunology, Vol 2, pages 125-136, 1995, or Racila et al, Journal of Experimental Medicine, Vol 181, pages 1539-1550, 1995.*

Hudson teaches as applied to claims 1-6 supra. Hudson fails to teach hypercrosslinking to make the antibody conjugates.

Marches et al. teaches that hypercrosslinking of antibody conjugates induces a significant increase in cell cycle arrest and apoptosis in virtually all antibodies.(see page 130, "Effect of Crosslinking IgM on lymphoma cells"). Racila et al. teaches that hypercrosslinking increases apoptosis. (See abstract)

Therefor it would have been prima facie obvious to one of ordinary skill in the art to combine the antibody conjugate of Hudson by hypercrosslinking, as taught by Marches et al. or Racila et al. and one would have been motivated to do so because hypercrosslinking increases cell cycle arrest and apoptosis, as taught by Marches et al. and Racila et al.

14. Claims 1-3, 6-9, 11-15, 18-23, 25, 43-45, 48-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Glennie, WO 91/03493, March 21, 1991*, in view of *Marches et al., Therapeutic Immunology, Vol 2, pages 125-136, 1995, or Racila et al, Journal of Experimental Medicine, Vol 181, pages 1539-1550, 1995.*

Glennie teaches as applied to claims 1-3, 6, 8-9, 11-15, 18-20, 22-23, 25, 43-45, 48, and 50-51 supra. Glennie fails to teach hypercrosslinking to make the antibody conjugates.

Marches et al. teaches that hypercrosslinking of antibody conjugates induces a significant increase in cell cycle arrest and apoptosis in virtually all antibodies.(see page 130, "Effect of Crosslinking IgM on lymphoma cells"). Racila et al. teaches that hypercrosslinking increases apoptosis. (See abstract)

Therefor it would have been prima facie obvious to one of ordinary skill in the art to combine the antibody conjugate of Glennie by hypercrosslinking, as taught by Marches et al. or Racila et al. and one would have been motivated to do so because hypercrosslinking increases cell cycle arrest and apoptosis, as taught by Marches et al. and Racila et al.

15. Claims 1, 3, and 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Ghetie et al., Exp. Opin. Invest. Drugs, Vol 5, No 3, pages 309-321*, in view of *Marches et al., Therapeutic Immunology, Vol 2, pages 125-136, 1995, or Racila et al, Journal of Experimental Medicine, Vol 181, pages 1539-1550, 1995.*

Ghetie et al. teaches as applied to claims 1, 3, and 6 supra. Ghetie et al. fails to teach hypercrosslinking to make the antibody conjugates.

Marches et al. teaches that hypercrosslinking of antibody conjugates induces a significant increase in cell cycle arrest and apoptosis in virtually all antibodies.(see page 130, "Effect of Crosslinking IgM on lymphoma cells"). Racila et al. teaches that hypercrosslinking increases apoptosis. (See abstract)

Therefor it would have been prima facie obvious to one of ordinary skill in the art to combine the antibody conjugate of Ghetie et al. by hypèrcrosslinking, as taught by Marches et al. or Racila et al. and one would have been motivated to do so because hypercrosslinking increases cell cycle arrest and apoptosis, as taught by Marches et al. and Racila et al.

16. Claims 1, 3, and 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Bosslet et al., US Patent 5,591,828, January 7, 1997.*, in view of *Marches et al., Therapeutic Immunology, Vol 2, pages 125-136, 1995, or Racila et al, Journal of Experimental Medicine, Vol 181, pages 1539-1550, 1995.*

Bosslet et al. teaches as applied to claims 1, 3, and 6 supra. Bosslet et al. fails to teach hypercrosslinking to make the antibody conjugates.

Marches et al. teaches that hypercrosslinking of antibody conjugates induces a significant increase in cell cycle arrest and apoptosis in virtually all antibodies.(see page 130, "Effect of Crosslinking IgM on lymphoma cells"). Racila et al. teaches that hypercrosslinking increases apoptosis. (See abstract)

Therefor it would have been prima facie obvious to one of ordinary skill in the art to combine the antibody conjugate of Bosslet et al. by hypercrosslinking, as taught by Marches et al. or Racila et al. and one would have been motivated to do so because hypercrosslinking increases cell cycle arrest and apoptosis, as taught by Marches et al. and Racila et al.

17. Claims 1-2, 6-7, 10-12, 18-21, and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Cumber et al., The Journal of Immunology, Vol 149, pages 120-126, July 1, 1992*, in view of *Marches et al., Therapeutic Immunology, Vol 2, pages 125-136, 1995, or Racila et al, Journal of Experimental Medicine, Vol 181, pages 1539-1550, 1995.*

Cumber et al. teaches as applied to claims 1-2, 6, 10-12, 18-20, and 23-24 supra. Cumber et al. fails to teach hypercrosslinking to make the antibody conjugates.

Marches et al. teaches that hypercrosslinking of antibody conjugates induces a significant increase in cell cycle arrest and apoptosis in virtually all antibodies.(see page 130, "Effect of Crosslinking IgM on lymphoma cells"). Racila et al. teaches that hypercrosslinking increases apoptosis. (See abstract)

Therefor it would have been prima facie obvious to one of ordinary skill in the art to combine the antibody conjugate of Cumber et al. by hypercrosslinking, as taught by Marches et al. or Racila et al. and one would have been motivated to do so because hypercrosslinking increases cell cycle arrest and apoptosis, as taught by Marches et al. and Racila et al.

18. Claims 1, 3, 7, 9, 11, 13, 21, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Bagshawe et al., US Patent 5,683,694, November 4, 1997*, in view of *Marches et al., Therapeutic Immunology, Vol 2, pages 125-136, 1995, or Racila et al, Journal of Experimental Medicine, Vol 181, pages 1539-1550, 1995.*

Bagshawe et al. teaches as applied to claims 1, 3, 9, 11, 13, and 23 supra. Bagshawe et al. fails to teach hypercrosslinking to make the antibody conjugates.

Marches et al. teaches that hypercrosslinking of antibody conjugates induces a significant increase in cell cycle arrest and apoptosis in virtually all antibodies.(see page 130, "Effect of Crosslinking IgM on lymphoma cells"). Racila et al. teaches that hypercrosslinking increases apoptosis. (See abstract)

Therefor it would have been prima facie obvious to one of ordinary skill in the art to combine the antibody conjugate of Bagshawe et al. by hypercrosslinking, as taught by Marches et al. or Racila et al. and one would have been motivated to do so because hypercrosslinking increases cell cycle arrest and apoptosis, as taught by Marches et al. and Racila et al.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Nichols, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell can be reached at (703) 308-4310. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**paulahutzell@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Nichols, Nee Hunt

January 31, 2000

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER